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Influence of Dose Rate Effects on Toxicity and Its Role in Human Risk Assessment

In many situations, human risk assessment relies on toxicity data from studies conducted in laboratory animals under standard testing protocols. Compounds are administered at constant dose levels over regular intervals (e.g. daily six hour inhalation) for defined periods of time (e.g. 13 weeks; 2 years). On the other hand, human exposures rarely conform to these prescriptive dosing regimes. As a matter of practical consequence, a number of default assumptions with respect to dose rate and exposure duration have become implemented in the assessment of risk. It is generally assumed that doses averaged over a work shift (in most occupational scenarios) or even a lifetime (in cancer risk assessments) result in equivalent risk regardless of exposure pattern. It is often assumed, for many toxicities (e.g. cancer; organ damage) that adverse response is linearly related to the product of dose level times duration (Haber's Law) so that, for example, 1 hour exposure to 80 ppm produces an equivalent effect to 8 hour exposure to 10 ppm. For other endpoints (e.g. irritation; some developmental effects), it is commonly assumed that dose level dominates and exposure duration has almost no influence on risk. Most of these default assumptions have not been rigorously supported by scientific research.

Recent improvement in our understanding of the underlying determinants of toxicity and the ability to make quantitative predictions should facilitate more focused research in the area of dose rate effects. Physiologically-based pharmacokinetic and dosimetry models are now able to relate the time course of a wide variety of internal dose metrics from a vast number of external exposure level and duration combinations. By accounting for time- and concentration-dependent processes, such as metabolism, these models should be useful in selecting experimental conditions and interpreting results. Better appreciation of the critical biochemical determinants of toxicity (e.g. interaction with molecular components; repair of cellular damage) provides a more informative framework in which to incorporate dose rate effects into risk assessment methodology. Finally, the existence of early cellular biomarkers of toxicity allows investigation of temporal relationships at lower and more relevant exposure levels. These advances are expected to permit the development of more scientifically sound approaches in accounting for exposure pattern and duration during estimation of human risk.

Background References

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